Principal Investigator/Program Director *(Last, first, middle)*: BROUWER, KIM L.R.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Brouwer, Kim L. Rowse	Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Oregon State University, Corvallis, OR	B.S.	1978	Pharmacy
University of Kentucky, Lexington, KY College of Pharmacy	Pharm.D. Ph.D.	1981 1983	Clinical Pharmacy Pharmacokinetics/ Pharmaceutical Science
University Kentucky, Lexington, KY College of Medicine, Dept. of Pharmacology	Post-Doctoral	1986	Drug Metabolism/ Pharmacology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE:

1978-1981 Hospital Pharmacy Residency; A.B. Chandler Medical Center, University of Kentucky
1978-1983 Graduate Teaching/Research Assistant; College of Pharmacy, University of Kentucky
1983-1986 Postdoctoral Fellow, College of Medicine, Department of Pharmacology, University of Kentucky
1997-present Professor, Div. of Drug Delivery & Disposition, School of Pharmacy, University of North Carolina (Assistant, 1986-1992; Associate, 1992-1997)
1997-present Professor, Curriculum in Toxicology, School of Medicine, University of North Carolina (Assistant, 1987-1992; Associate, 1992-1997)
1996-present Director of Graduate Studies, School of Pharmacy, University of North Carolina at Chapel Hill

HONORS: National Rho Chi Graduate Scholarship, 1978; National Alpha Lambda Delta Alice Crocker Lloyd Graduate Fellow, 1980; American Foundation for Pharmaceutical Education Fellow, 1981-1982; Smith Kline Beckman Pharmaceutics/Biopharmaceutics AFPE Fellow, 1982-1983; American Association of Colleges of Pharmacy Young Investigators Program Grant Recipient, 1986-1987; PMA Foundation Research Starter Grant Recipient, 1987; Hollingsworth Faculty Scholar, UNC School of Pharmacy, 1995-1997; Fellow, American Association of Pharmaceutical Scientists, 1998; NIH Pharmacology Study Section Member, 1998-2002; PhRMA Foundation Award in Excellence in Pharmaceutics, 2001.

PUBLICATIONS: (selected from 87 refereed articles, 128 published abstracts, 3 book chapters)

Brouwer, KLR and Jones, JA: Altered Hepatobiliary Disposition of Acetaminophen Metabolites Following Phenobarbital Pretreatment and Renal Ligation: Evidence for Impaired Biliary Excretion and a Diffusional Barrier. *J Pharmacol Exp Ther* 252:657-664, 1990.

Shea, T, Graham, M, Bernard, S, Steagall, A, Wiley, J, Serody, J, Brecher, M, Bentley, S, Johnston, C, Vaisman, A, Chaney, S, Letrent, S and Brouwer, KLR: A Clinical and Pharmacokinetic Study of High-Dose Carboplatin, Paclitaxel, Granulocyte Colony-Stimulating Factor, and Peripheral Blood Stem Cells in Patients with Unresectable or Metastatic Cancer. *Seminars in Oncology*. 22 (Suppl 12): 80-85, 1995.

Moore, KHP, Raasch, RH, Brouwer, KLR, Opheim, K, Lemon, SM and van der Horst, CM: Pharmacokinetics and Bioavailability of Zidovudine and Its Glucuronidated Metabolite in Patients with Human Immunodeficiency Virus Infection and Hepatic Disease (AIDS Clinical Trials Group Protocol 062). *Antimicrob Agents Chemother* 39:2732-2737, 1995.

Booth, CL, Pollack, GM and Brouwer, KLR: Hepatobiliary Disposition of Valproic Acid and Valproate Glucuronide: Use of a Pharmacokinetic Model to Examine Rate-Limiting Steps & Potential Sites of Drug Interactions. *Hepatology* 23:771-780, 1996.

Matheny, CJ, Taft, DR, Brouwer, KLR and Pollack, GM: Evidence for Reversible Sequestration of Morphine in Rat Liver. *Biochem Pharmacol* 52: 535-541, 1996.

Peckman, HJ, Dupuis, RE, Sawyer, WT, Brouwer, KLR and Cross, RE: Vancomycin Serum Concentrations in Patients with Renal Dysfunction: A Comparison of FPIA and EMIT. *Ther Drug Monit.* 18:647-653, 1996.

Carlton, LD, Pollack, GM and Brouwer, KLR: Physiologic Pharmacokinetic Modeling of Gastrointestinal Blood Flow as a Rate-Limiting Step in the Oral Absorption of Digoxin: Implications for Patients with Congestive Heart Failure Receiving Epoprostenol. *J Pharm Sci* 85: 473-477, 1996.

Brouwer, KLR and Thurman RG: Isolated Perfused Liver. *Pharm Biotech* 8:161-92, 1996.

Mosley, AK and Brouwer KLR. Heat Treatment of Human Serum to Inactivate HIV Does Not Alter Protein Binding of Selected Drugs. *Ther Drug Monit* 19:477-479, 1997.

Nolting, A, DeLong RK, Fisher, MH, Wickstrom, E, Pollack, GM, Juliano, RL and Brouwer, KLR: Hepatic Distribution and Clearance of Antisense Oligonucleotides in the Isolated Perfused Rat Liver. *Pharm Res* 14:516-521, 1997.

Farthing, D, Brouwer, KLR, Fakhry, I and Sica, D: Solid-Phase Extraction and Determination of Ranitidine in Human Plasma by a High Performance Liquid Chromatographic Method Utilizing Midbore Chromatography. *J Chromatogr B. Biomed Sci Appl* 688:350-353, 1997.

Turner, KC and Brouwer, KLR.: *In Vitro* Mechanisms of Probenecid-Associated Alterations in Acetaminophen Glucuronide Hepatic Disposition. *Drug Metab Dispos* 25:1017-1021, 1997.

Noone, PG, Regnis, JA, Liu, X, Brouwer, KLR, Robinson, M, Edwards, L and Knowles, MR Airway Deposition and Clearance, and Systemic Pharmacokinetics of Amiloride Following Aerosolization With an Ultrasonic Nebulizer to Normal Airways. *Chest* 112:1283-1290, 1997.

Letrent, SP, Pollack, GM, Brouwer KR and Brouwer, KLR: Effect of GW918, a Potent P-Glycoprotein Inhibitor, on Morphine Pharmacokinetics and Pharmacodynamics in the Rat. *Pharm Res* 15:599-605, 1998.

Liu, X, Brouwer, KLR, Gan, L-SL, Brouwer, KR, Stieger, B, Meier, PJ, Audus, KL and LeCluyse, EL: Partial Maintenance of Taurocholate Uptake by Adult Rat Hepatocytes Cultured in Collagen Sandwich Configuration. *Pharm Res* 15:1533-1539, 1998.

Booth, CL, Brouwer, KR and Brouwer, KLR: Effect of Multidrug Resistance Modulators on the Hepatobiliary Disposition of Doxorubicin in the Isolated Perfused Rat Liver. *Cancer Res* 58:3641-3648, 1998.

Socinski, MA, Mudd, PN, Radomski, KM, Steagall, A, Lawrence, P, Bernard, S, Letrent, SP, Gonzalez P, and Brouwer, KLR: Phase I Trial of a 96-hour Paclitaxel Infusion with Filgrastim Support in Refractory Solid Tumor Patients. *Anti-Cancer Drugs* 9:611-619, 1998.

Reynolds, KS, Song, M, Heizer, WD, Burns, CB, Sica, DA and Brouwer, KLR: Effect of Pancreatico-Biliary Secretions and GI Transit Time on the Absorption and Pharmacokinetic Profile of Ranitidine in Humans. *Pharm Res* 15:1281-1285, 1998.

Pithavala, YK, Heizer, WD, Parr, AF, O'Connor-Semmes, RL and Brouwer, KLR: Use of the *InteliSite*® Capsule to Study Ranitidine Absorption from Various Sites Within the Human Intestinal Tract. *Pharm Res* 15:1869-1875, 1998.

Liu, X, LeCluyse, EL, Brouwer, KR, Gan, LL, Lemasters, JJ, Stieger, B, Meier, PJ and Brouwer, KLR: Biliary Excretion in Primary Rat Hepatocytes Cultured in a Collagen-Sandwich Configuration. *Am J Physiol* 277(*Gastrointest Liver Physiol* 40):G12-21, 1999.

Liu, X, LeCluyse, EL, Brouwer, KR, Lightfoot, RM, Lee, JI and Brouwer, KLR: Use of Ca^{2+} Modulation to Evaluate Biliary Excretion in Sandwich-Cultured Rat Hepatocytes. *J Pharmacol Exp Ther* 289:1592-1599, 1999.

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Letrent, SP, Pollack, GM, Brouwer, KR and Brouwer KLR: Effects of a Potent and Specific P-glycoprotein Inhibitor on the Blood-Brain Barrier Distribution and Antinociceptive Effect of Morphine in the Rat. *Drug Metab Dispos* 27:827-834, 1999.

Letrent, SP, Polli, J, Humphreys, J, Pollack, GM, Brouwer, KR and Brouwer, KLR: P-glycoprotein-Mediated Transport of Morphine in Brain Capillary Endothelial Cells. *Biochem Pharmacol* 58:951-957, 1999.

Aquilante, CL, Letrent SP, Pollack, GM and Brouwer, KLR: Increased Brain P-Glycoprotein in Morphine Tolerant Rats. *Life Sci*, 66:PL 47-51, 2000.

Fischer, JD, Song, MH, Suttle, AB, Heizer, WD, Burns, CB, Vargo, DL and Brouwer, KLR: Comparison of Zafirlukast (Accolate®) Absorption After Oral and Colonic Administration in Humans. *Pharm Res* 17:154-159, 2000.

Xiong, H, Turner, KC, Ward, ES, Jansen, PLM and Brouwer, KLR: Altered Hepatobiliary Disposition of Acetaminophen Glucuronide in Isolated Perfused Livers from Multidrug Resistance-Associated Protein 2-Deficient TR$^-$ Rats. *J Pharmacol Exp Ther* 295:512-518, 2000.

Ward, ES, Pollack, GM and Brouwer, KLR: Probenecid-Associated Alterations in Valproic Acid Pharmacokinetics in Rats: Can *In Vivo* Disposition of Valproate Glucuronide Be Predicted from *In Vitro* Data? *Drug Metab Dispos.* 28:1433-1439, 2000.

Ward, ES, Pollack, GM and Brouwer, KLR: Probenecid-Associated Alterations in Valproate Glucuronide Hepatobiliary Disposition: Mechanistic Assessment Utilizing Mathematical Modeling. *J Pharmacol Exp Ther* 297:141-147, 2001.

Chandra, P, LeCluyse, EL and Brouwer, KLR: Optimization of Culture Conditions for Determining Hepatobiliary Disposition of Taurocholate in Sandwich-Cultured Rat Hepatocytes. *In Vitro Cellular & Developmental Biology* 37:380-385, 2001.

Crews, KR, Murthy, BP, Hussey, EK, Passannante, AN, Palmer, JL, Maixner, W and Brouwer, KLR: Lack of Effect of Ondansetron on the Pharmacokinetics and Analgesic Effects of Morphine and Metabolites after Single-Dose Morphine Administration in Healthy Volunteers. *Br J Clin Pharmacol* 51:309-316, 2001.

Matheney, CJ, Lamb, MW, Brouwer, KLR and Pollack, GM: Pharmacokinetic and Pharmacodynamic Implications of P-glycoprotein Modulation. *Pharmacother* 21:778-796, 2001.

Annaert, PP, Turncliff, R, Booth, CL, Thakker, DR and Brouwer, KLR: P-glycoprotein-Mediated *In Vitro* Biliary Excretion in Sandwich-Cultured Rat Hepatocytes. *Drug Metab Dispos* 29:1277-1283, 2001.

Xiong, H, Yoshinari, K, Brouwer, KLR, and Negishi, M: Role of Constitutive Androstane Receptor in the *In Vivo* Induction of Mrp3 and CYP2B1/2 by Phenobarbital. *Drug Metab Dispos* 30:918-923, 2002.

Xiong, H, Suzuki, H, Sugiyama Y, Meier PJ, Pollack GM and Brouwer, KLR: Mechanisms of Impaired Biliary Excretion of Acetaminophen Glucuronide After Acute Phenobarbital Treatment or Phenobarbital Pretreatment: *Drug Metab Dispos* 30:962-969, 2002.

Lee, K, Chee, N, Brouwer KLR, Thakker DR: Secretory Transport of Ranitidine and Famotidine across Caco-2 Cell Monolayers. *J Pharmacol Exp Ther* 303:574-580, 2002.

Murthy, BR, Pollack, GM, and Brouwer, KLR. Contribution of Morphine-6-glucuronide to Antinociception Following Intravenous Administration of Morphine to Healthy Volunteers. *J Clin Pharmacol* 42:569-76, 2002.

Zamek-Gliszczynski, MJ, Xiong, H, Patel, NJ, Turncliff, RZ, Pollack, GM, and Brouwer, KLR: Pharmacokinetics of 5 (and 6)-Carboxy-2',7'-Dichlorofluorescein and Its Diacetate Promoiety in the Liver. *J Pharmacol Exp Ther* 304: 801-809, 2003.

McRae, MP, Brouwer, KLR, and Kashuba, AK: Cytokine Regulation of P-Glycoprotein. *Drug Metab Rev* in press, 2003.

Patel, NJ, Zamek-Gliszczynski, MJ, Zhang, P, Han, Y-H, Jansen, PLM, Meier, PJ, Stieger, B, and Brouwer, KLR: Phenobarbital Alters Hepatic Mrp2 Function by Direct and Indirect Interactions. *Mol Pharm* in press, 2003.

RESEARCH PROJECTS ONGOING OR COMPLETED DURING THE LAST THREE YEARS:

Ongoing Research Support

Title: Altered Hepatic Disposition of Anionic Drugs: Mechanisms
Principal Investigator: Brouwer, K.L.R.
Agency: NIGMS, NIH.
Type: Research Grant (R01 GM41935-10-13) Period: 07/01/01-06/30/05

The objective of this research program is to develop a mechanistic understanding of how perturbations in hepatic transport systems influence overall hepatobiliary disposition of anionic drugs and derived metabolites. A multiexperimental approach utilizing *in vivo*, isolated perfused rat liver, and *in vitro* cellular systems, including both rat and human hepatocytes, is being used to elucidate mechanisms of altered function of hepatic organic anion transport systems, predict alterations in hepatobiliary drug disposition and drug transport interactions.

Title: P-Glycoprotein Induction: Kinetic/Dynamic Implications
Principal Investigator: Pollack, G.M.
Co-Investigator: Brouwer, K.L.R.
Agency: NIGMS, NIH.
Type: Research Grant (R01 GM61191 1-4) Period: 4/1/01-3/31/05

The long-term goals of this research program are to explore the hypothesis that inducers of P-glycoprotein cause clinically relevant alterations in the disposition and action of P-glycoprotein substrates.

Title: Development of an *In Vitro*, Moderate-Throughput Screening Assay to Predict Hepatobiliary Disposition of Drug Candidates
Principal Investigator: Brouwer, K.L.R.
Agency: Pfizer, Inc.
Type: Research Grant Period: 10/22/01-10/21/04

The objective of the studies outlined in this research project is to develop an *in vitro,* moderate-thoughput screening model for rat and human hepatocytes that could be used to: (1) identify compounds that undergo extensive hepatic uptake and biliary excretion, and (2) accurately predict *in vivo* biliary clearance of drugs in rats and humans.

Completed Research Support

Title: *In Vitro* Methods to Examine Hepatobiliary Disposition of BILN 2061 ZW
Principal Investigator: Brouwer, K.L.R.
Agency: Boehringer Ingelheim
Type: Research Grant Period: 02/01/02-01/31/03

The objectives of this research collaboration include: (1) development and application of *in vitro* methodology to predict the hepatobiliary disposition of selected compounds (BILN 2061 ZW and analogs), (2) evaluation of the correlation between the biliary clearance of selected compounds *in vitro* and *in vivo*, and (3) identification of the basolateral and canalicular hepatic transport proteins responsible for the hepatic uptake and biliary excretion of selected compounds. In addition, the function of hepatic transport proteins in human hepatocytes from diseased livers will be examined, pending availability of tissue.

Title: Testing Two Pfizer Compounds in TR$^-$ Rats
Principal Investigator: Brouwer, K.L.R.
Agency: Pfizer, Inc.
Type: Research Contract Period: 02/28/00-05/27/00

The *in vivo* disposition and biliary excretion of two new chemical entities were characterized in control and mutant TR$^-$ rats to determine if these compounds were substrates for Mrp2.